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EXAMINER
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BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Paper No. 35

Serial Number: 08/478748
Filing Date: 6/7/95
Appellant(s): Thomas Waldmann

Dorothy Auth
For Appellant

EXAMINER'S ANSWER

This is in response to appellant's Brief on appeal filed 4/30/01 (Paper No. 34).

The text of those sections of Title 35 U.S. Code not included in this appeal can be found in a previous Office Action herein.

(1) Real Party of Interest.

A statement identifying the real party of interest in contained in the Brief.

(2) Related Appeals and Interferences Identified.

A statement identifying that no related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the Brief.

(3) Status of Claims.

The statement of the status of claims contained in the Brief is correct.

This appeal involves claim 27.

(4) Status of Amendments After Final.

Appellant's statement of the status of amendments after final rejection contained in the Brief is correct.

(5) Summary of Invention.

The summary of invention contained in the Brief is correct.

As pointed out previously, for examination purposes given the claimed recitation; all that is required of the prior art is to provide a dosage of mCi and an amount of ^{90}Y-conjugated anti-Tac antibody to a patient with one of the soluble IL-2 receptor (IL-2R) levels.

It is not necessary that the prior art provide all of the dosages and amounts and ^{90}Y-conjugated anti-Tac antibody to a patient(s) with all of the soluble IL-2R levels; nor it is necessary for the prior art to predetermine the three dosage/amount/soluble level determinations set for in the claimed methods. Given the treatment of human patients who express IL-2R-expressing disorders and the nature of clinical trials; it would have been routine for the ordinary artisan at the time the invention was made to determine soluble IL-2R prior to treating or administering ^{90}Y-conjugated anti-Tac antibody to such patients.

(6) Issues.

The appellant's statement of the issues in the Brief is correct.

Also note there are alternative interpretations of the claimed method.

(7) Grouping of Claims.

Only one claim, claim 27, is at issue.

(8) Claims Appealed.

The copy of the appealed claims contained in the Appendix to the Brief is correct.

(9) Prior Art of Record.

1) Rubin et al., Ann. Int. Med. 113: 619 -627, 1990.
2) Vissendorf et al., Int. J. Radiation Oncology 22:37-45, 1991.
3) Waldmann, Blood 82: 1701-1712, 1993.
4) Waldmann, Leukemia 7, Suppl 2 : S151-S156, 1993.
5) Waldmann et al., Important Adv. Oncol., 1994.
6) Waldmann, Ann. Oncol. 5: 13-17, 1994.
7) Waldmann et al., Blood 86: 4063-4075, 1995.

(10) Grounds of Rejection.

The following ground(s) of rejection are applicable to the appealed claims.

Rejection Under 35 U.S.C. § 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. § 103(a) as obvious

Claim 27 stands rejected under 35 U.S.C. § 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. § 103 as obvious Waldmann (Blood 82: 1701-1712, 1993; 892), as evidenced by Waldmann et al. (Blood 86: 4063-4075, 1995) AND/OR Vissendorf et al. (Int. J. Radiation Oncology 22:37-45, 1991).

Waldmann et al. (1993) teach administering 5 - 15 mCi doses of ^{90}Yttrium (^{90}Y) - labeled anti-Tac antibody (^{90}Y) anti-Tac antibody to achieve remission in treating adult T cell leukemia (ATL) patients in a dose-escalation trial (see page 1711, column 1, paragraph 1 of Waldmann, Blood 1993) including the determination of soluble IL-2 receptor (IL-2R) levels, encompassed by the claimed methods (see entire document, including Materials and Methods such as the Therapeutic Study Plan, Results including Tables 1 and 2, Discussion). Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced therapeutic modalities.

In the alternative, it would have obvious to give 20 mg of anti-Tac comprising 5-15 mCi ^{90}Yttrium (^{90}Y) to patients with soluble IL-2R levels of greater than 50,000 given the clinical results / duration of the different patients in these studies. From the teachings of the reference, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

The evidentiary references Waldmann et al. (Blood 86: 4063-4075, 1995) AND/OR Vissendorf et al. (Int. J. Radiation Oncology 22:37-45, 1991) have been provided to support that the inherency of prior art teaching of administering 5 - 15 mCi doses of ^{90}Y-labeled anti-Tac antibody to achieve remission in treating patients with adult T cell leukemia (ATL) (see page 1711, column 1, paragraph 1 of Waldmann, Blood 1993) encompasses the total amount of 2-20 mg anti-Tac encompassed by the claimed methods.

Waldmann et al. (Blood 86: 4063-4075, 1995) (see entire document, including the Introduction, particularly page 4064, column 1, and the Therapeutic Study Plan in the Materials and Methods) disclose that the Phase I trials disclosed in the Waldmann (Blood, 1993) teaching led to algorithm which was the basis for the regimen encompassed by the claimed methods. Therefore, given that the algorithm which was the basis for the regimen encompassed by the claimed methods relied upon observations from these Phase I studies; it would be inherent that the dosing and successful treatment of adult T cell leukemia patients set forth in the Phase I studies would meet the claimed dosage/amount/soluble level determinations.

Vissendorf et al. (Int. J. Radiation Oncology 22:37-45, 1991) teach specific activities for ^{90}Y-labeled antibodies was 5-40 mCi per mg protein. Therefore, the prior art teaching of 5 - 15 mCi doses of ^{90}Y anti-Tac antibody would meet the 2-20 mg ^{90}Y-labeled anti-Tac encompassed by the claimed methods.

Rejection Under 35 U.S.C. § 103(a)

Claim 27 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over Waldmann (Blood 82: 1701-1712, 1993) AND/OR Waldmann et al. (Important Adv. Oncol. 131-141, 1994) AND/OR Waldmann (Leukemia 7, Suppl 2 : S151-S156, 1993) AND/OR Waldmann (Ann. Oncol. 5: 13-17, 1994) in view of Vissendorf et al. (Int. J. Radiation Oncology 22:37-45, 1991) and Rubin et al. (Ann. Int. Med. 113: 619 - 627, 1990).

The teachings of Waldmann (Blood 82: 1701-1712, 1993) , Waldmann et al. (Important Adv. Oncol. 131-141, 1994), Waldmann (Leukemia 7, Suppl 2 : S151-S156, 1993) AND/OR Waldmann (Ann. Oncol. 5: 13-17, 1994) are all of record.

Waldmann et al. teach administering 5 - 15 mCi doses of ^{90}Yttrium (^{90}Y) - labeled anti-Tac antibody (^{90}Y) anti-Tac antibody to achieve remission in treating adult T cell leukemia (ATL) patients in a dose-escalation trial (see page 1711, column 1, paragraph 1 of Waldmann, Blood 1993) including the determination of soluble IL-2R levels, encompassed by the claimed methods (see entire document, including Materials and Methods such as the Therapeutic Study Plan, Results including Tables 1 and 2, Discussion).

In teaching the advantages of radiolabled monoclonal antibodies as immunoconjugates to deliver cytotoxic agents to target cells (page 137, column 2, paragraph 1); Waldmann et al. (Important Adv. Oncol., 1994) (see entire document) teach a Phase I dose escalation clinical trial and a subsequent Phase II trial of administering 5 - 15 mCi doses of ^{90}Y - labeled anti-Tac antibody to achieve remission in treating adult T cell leukemia (ATL) patients (see page 138, columns 1-2, overlapping paragraph). It is noted that this particular Waldmann reference discloses µg amounts of ^{90}Y rather than mg amounts of ^{90}Y . Given the other teachings by Waldmann et al. of record and cited herein, where it appears that the same or nearly the same ^{90}Y anti-Tac clinical trials are disclosed; the disclosure of µg amounts of ^{90}Y anti-Tac was clearly a typographical error on the part of the Important Advances in Oncology 1994. Here, Waldmann also discloses the initiation of an additional trial of employing humanized anti-Tac which is less immunogenic than murine anti-Tac to extend the patient populations to include IL-2 receptor (IL-2R) - expressing lymphomas. Waldmann also teach that it was known that the serum concentrations of the soluble form of IL-2Rα was elevated in patients with disorders encompassing leukemias, lymphomas and allograft rejection (page 132, column 2).

Waldmann (Leukemia 7, Suppl 2 : S151-S156, 1993) (see entire document) teach a dose escalation clinical trial of administering 5. 10 and 15 mCi doses of ^{90}Y - labeled anti-Tac antibody to achieve remission in treating HTLV-I-associated Tac-expressing adult T cell leukemia (ATL) patients (see page 154, column 1). Waldmann also teach that it was known that the serum concentrations of the soluble form of IL-2Rα was elevated in patients with disorders encompassing lymphoid neoplasia, select autoimmune diseases and in individuals rejecting allografts (page S152, columns 1-2; IL-2R Expression in Malignancy).

Waldmann (Ann. Oncol. 5: 13-17, 1994) teach a Phase I dose escalation clinical trial and a subsequent Phase II trial of administering 5 - 15 mCi doses of ^{90}Y - labeled anti-Tac antibody to achieve remission in treating adult T cell leukemia (ATL) patients (see page 138, columns 1-2, overlapping paragraph). Here, Waldmann also discloses the initiation of an additional trial of employing humanized anti-Tac which is less immunogenic than murine anti-Tac to extend the patient populations to include IL-2R-receptor-expressing lymphomas. Waldmann also teach that it was known that the serum concentrations of the soluble form of IL-2Rα was elevated in patients with disorders encompassing lymphoid neoplasia, select autoimmune diseases and in individuals rejecting allografts (page S14; IL-2R Expression in Malignancy).

These Waldmann references all teach a dose escalation clinical trial of administering 5 - 15 mCi doses of ^{90}Y - labeled anti-Tac antibody to achieve remission in treating adult T cell leukemia (ATL) patients and that it was known at the time the invention was made that the serum concentrations of the soluble form of IL-2Rα was elevated in patients with disorders encompassing lymphoid neoplasia, select autoimmune diseases and in individuals rejecting allografts (see citations above).

These Waldmann teachings differ from the claimed methods by not disclosing the particular mg amount of the 5 - 15 mCi doses of ^{90}Y anti-Tac antibody.

Vissendorf et al. (Int. J. Radiation Oncology 22:37-45, 1991) teach specific activities for ^{90}Y - labeled antibodies was 5-40 mCi per mg protein. Therefore, the prior art teaching of 5 - 15 mCi doses of ^{90}Y anti-Tac antibody would have been expected to meet the 2-20 mg anti-Tac encompassed by the claimed methods.

These Waldmann et al. references differ from the claimed methods by not disclosing the particular ranges of ^{90}Y anti-Tac antibody dosages as they would read on soluble IL-2R levels.

Waldmann (Blood 1993) clearly teaches that various types of ATL have circulating IL-2R/Tac encompassed by the claimed methods (See Table 1 on page 1703).

Similarly, the other Waldmann references teach elevated levels of the soluble IL-2R was associated with neoplastic disorders (e.g. page 132, column 2 to page 134, column 1 of Waldmann, Important Advances in Oncology, 1994; page S14 of Waldmann, Annals of Oncology, 1994 and page S152, columns 1-2; IL-2R Expression in Malignancy of Waldmann, Leukemia 7, Suppl 2 : S151-S156, 1993).

In addition, Rubin et al. (Ann. Intern. Med., 1990) reviews that soluble IL-2 receptors were measured in a number of human diseases, including the malignancies encompassed by the claimed invention (see entire document, including page 621-622 and Table 1).

Therefore, the soluble IL-2 receptor levels encompassed by the claimed methods were expected levels of malignant patients at the time the invention was made.

Further, the Waldmann articles all disclose the association of IL-2 receptors and various diseases encompassed by the claimed invention as well as it was important to maintain the activity levels of anti-Tac antibody therapies in treating such diseases (see entire documents). The combined references of record also address the importance of pharmacokinetic analyses. Therefore, it would have been obvious to one of ordinary skill in the art to select for appropriate amounts of radiolabeled anti-Tac antibody (e.g. mg and mCi of anti-Tac antibodies) in vivo to achieve therapeutic efficacy in the face of soluble IL-2 receptors in patients. It would have been recognized that there would have been a range of therapeutic doses since differences in the nature of diseases as well as individual patients were known and expected in the art at the time the invention was made.

Again as pointed out previously and above, it is not necessary that the prior art provide all of the dosages and amounts and ^{90}Y-conjugated anti-Tac antibody to a patient with all of the soluble IL-2R levels; nor it is necessary for the prior art to predetermine the three dosage/amount/soluble level determinations set for in the claimed methods

For examination purposes, given the claimed recitation; all that is required of the prior art is to provide a dosage of mCi and an amount of ^{90}Y-conjugated anti-Tac antibody to a patient with one of the soluble IL-2R levels.

Given the treatment of human patients who express IL-2R-expressing disorders and the nature of clinical trials; it would have been routine for the ordinary artisan at the time the invention was made to determine soluble IL-2R prior to treating or administering ^{90}Y-conjugated anti-Tac antibody to such patients.

Also, the combined references clearly taught the efficacy of ^{90}Y-labeled anti-Tac antibody therapies including human patients and that a certain amount of mg of ^{90}Y-labeled antibody was associated with a certain activity (e.g. mCi) of said antibody; therefore, it would have been expected that the ordinary artisan would have administered 5-15 mCi of ^{90}Y-labeled anti-Tac antibody in total amounts of 2-20 mg to patients.

Also, given that the known advantage of radiolabeled antibodies over unlabeled antibodies at the time the invention was made was the ability to deliver a more effective means of delivering a therapeutic dose or radiation via the ^{90}Yttrium label. Therefore, it would have been expected that ^{90}Y-labeled anti-Tac antibodies would require less than the 20-50 mg doses of unlabeled anti-Tac antibody in the treatment of diseases associated with Tac-positive cells (e.g. malignant cells).

Also, the prior art teaches the use of chimeric/humanized anti-Tac antibodies, which also would be expected to alleviate the HAMA (human anti-murine antibody) responses to unlabeled murine anti-Tac antibodies and, in turn, would have been expected to require less than the 20-50 mg doses of unlabeled anti-Tac antibody in the treatment of diseases associated with Tac-positive cells (e.g. malignant cells).

This would have resulted in the effective dosages encompassed by the claimed limitations, including the amount of mg/mCi of anti-Tac antibody to achieve a therapeutic effect, wherein in certain cases IL-2 receptor saturation levels would have been achieved at the time the invention was made.

As indicated previously, the references clearly teach the same amount or nearly the same amount of ^{90}Y- labeled anti-Tac antibody for the same methods as presently claimed. The claimed effective dosages are either taught by the references or it would have obvious to one of ordinary skill in the art at the time the invention was made that such amounts of mg/mCi of ^{90}Y- labeled anti-Tac antibody as well as IL-2 receptor levels would have been met by the administration of 5-15 mCi of ^{90}Y- labeled anti-Tac antibody in patients having disease associated with elevated levels of IL-2 receptor-/Tac-positive cells.

Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to administer a dosage of mCi and an amount of ^{90}Y-conjugated anti-Tac antibody to a patient with one of the soluble IL-2R levels encompassed by at least one of the three parameters encompassed by the claimed methods to treat and achieve remission in patients with hematologic IL2R-expressing malignancies. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention was a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

(11) Response to Argument

Rejection Under 35 U.S.C. § 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. § 103(a) as obvious

Claim 27 stands rejected under 35 U.S.C. § 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. § 103 as obvious Waldmann (Blood 82: 1701-1712, 1993; 892), as evidenced by Waldmann et al. (Blood 86: 4063-4075, 1995) AND/OR Vissendorf et al. (Int. J. Radiation Oncology 22:37-45, 1991).

Appellant's arguments including the Waldmann declaration under 37 C.F.R. § 1.132 filed 3/2/99 (Paper No. 23) have been fully considered but are not found convincing in that Waldmann (Blood, 1993) appears to teach treating and achieving remission in adult T cell leukemia patients with ^{90}Yttrium (^{90}Y)-labeled anti-Tac antibody in the dosages ranges including the determination of soluble IL-2 receptor (IL-2R) levels, encompassed by the claimed methods.

Again, as pointed out previously and herein for examination purposes given the claimed recitation; all that is required of the prior art is to provide a dosage of mCi and an amount of ^{90}Y-conjugated anti-Tac antibody to a patient with one of the soluble IL-2R levels.

It is not necessary that the prior art provide all of the dosages and amounts and ^{90}Y-conjugated anti-Tac antibody to a patient with all of the soluble IL-2R levels; nor it is necessary for the prior art to predetermine the three dosage/amount/soluble level determinations set for in the claimed methods.

Appellant's claimed methods recite various levels of ^{90}Y anti-Tac antibody based in patients having different soluble IL-2R levels. The prior art does not have to meet each asserted level, provided it meets one of the ranges of ^{90}Y anti-Tac antibody / soluble IL-2R levels.

Again, a species will anticipate a claim to a genus. See MPEP 2131.02.

Appellant argues that Waldmann et al. (1993) describes the use of unlabeled anti-Tac antibodies in patients with human adult T cell leukemia with varying levels of soluble IL-2R levels.

Appellant does acknowledge that page 1710, column 1, paragraph 1 of Waldmann et al. (1993) discloses that "using radiolabeled anti-Tac in conjunction with unmodified anti-Tac, only 2-17 mg of infused anti-Tac antibody per patient is required to yield circulating bioavailable anti-Tac antibody that can bind to IL2R-/Tac- expressing ATL cells" and that page 1711, column 1, of Waldmann et al. (1993) describes that "conjugating anti-Tac with cytotoxic agents, such as 5-15 mCi ^{90}Yttrium., was employed to improve the effectiveness of IL-2R-directed therapy of ATL".

Appellant argues in conjunction with Continental Can Co. USA, Inc. v. Monsanto Co. that the "missing descriptive matter is necessarily present in the thing described in the reference and so recognized by persons of ordinary skill".

Appellant asserts that the claimed method requires the important step of determining the dosage and administering the dosage to the patient to eliminate the disease-associated Tac-positive cells.

Again, as pointed out previously and herein for examination purposes given the claimed recitation; all that is required of the prior art is to provide a dosage of mCi and an amount of ^{90}Y-conjugated anti-Tac antibody to a patient with one of the soluble IL-2R levels.

It is not necessary that the prior art provide all of the dosages and amounts and ^{90}Y-conjugated anti-Tac antibody to a patient with all of the soluble IL-2R levels; nor it is necessary for the prior art to predetermine each of the three dosage/amount/soluble level determinations set for in the claimed methods.

Given the treatment of human patients who express IL-2R-expressing disorders and the nature of clinical trials; it would have been routine for the ordinary artisan at the time the invention was made to determine soluble IL-2R prior to treating or administering ^{90}Y-conjugated anti-Tac antibody to such patients.

Appellant's claimed methods recite various levels of ^{90}Y anti-Tac antibody based in patients having different soluble IL-2R levels. The prior art does not have to meet each asserted level, provided it meets at least one of the points within the claimed ranges of ^{90}Y anti-Tac antibody / soluble IL-2R levels.

Appellant asserts that Waldmann et al. (1993) reference does not make a distinction regarding dosages based upon soluble IL-2R levels in the patients and teach therapeutic amounts rather than minimum amounts needed to have circulating bioavailable anti-Tac antibody.

Again, appellant focuses on the results or statements in Waldmann et al. (1993) concerning the use of unlabeled anti-Tac antibody to achieve therapeutic results, including maintaining receptor saturation.

Appellant argues in conjunction with Hansgirg v. Kemmer and Continental Can Co. v. Monsanto Co. that inherency may not be established by probabilities or possibilities.

Appellant argues in conjunction with In re Newell and Sensonics, Inc. v. Aerosonic Corp. that the inappropriateness of taking a retrospective view or hindsight knowledge of the prior art.

Appellant argues in conjunction with Continental Can Co. v. Monsanto Co. that an anticipatory reference must teach every element of a claim either expressly or under the doctrine of inherency.

Appellant asserts that the reliance upon the evidentiary Waldmann et al. (1995) reference is seriously flawed.

Here again, appellant focuses on the dosing determination / regimen as claimed and focuses on the use of unlabeled anti-Tac antibody cited in the primary reference Waldmann et al. (1993)

However in contrast to appellant's reliance upon the teaching of unlabeled anti-Tac antibodies; Waldmann et al. (1993) clearly teach administering 5 - 15 mCi doses of ^{90}Y - labeled anti-Tac antibody to achieve remission in treating adult T cell leukemia (ATL) patients in a dose-escalation trial (see page 1711, column 1, paragraph 1 of Waldmann, Blood 1993) including the determination of soluble IL-2R levels, encompassed by the claimed methods (see entire document, including Materials and Methods such as the Therapeutic Study Plan, Results including Tables 1 and 2, Discussion). Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced therapeutic modalities.

Here, the prior art treatment of adult T cell leukemia patients, eight of which underwent a partial remission and two of which underwent complete remission following ^{90}Y anti-Tac antibody therapy (page 1710, column 1; paragraph 1), would have the inherent property of meeting at least one of three dosage / parameter levels encompassed by the claimed invention.

Appellant argues that Waldmann et al. (1995) is not prior art and does not constitute prior art under the 35 U.S.C. § 102(b) and 35 U.S.C. § 103 statutes.

With respect to the post-filing date reference Waldmann et al. (1995); it is noted the Waldmann et al. (1993) is the prior art reference and that Waldmann et al. (1995) is provided simply to show an inherent property of the prior art methods. Waldmann et al. (1995) is not being applied as a prior art reference. Also, see MPEP 2124. In some circumstances, a later publication showing factual evidence can be cited includes situations where the facts shown in the reference are evidence that, as of an application filing date, undue experimentation would have been required.

Here, Waldmann et al. (Blood 86: 4063-4075, 1995) (see entire document, including the Introduction, particularly page 4064, column 1, and the Therapeutic Study Plan in the Materials and Methods) disclose that the Phase I trials disclosed in the primary reference Waldmann (Blood, 1993) led to algorithm which was the basis for the regimen encompassed by the claimed methods, as they read on a determination dosing regimen of administering ^{90}Y anti-Tac antibody at different dosages based upon a patient's soluble IL-2R levels.

Therefore, given that the Phase I clinical trials disclosed in the primary Waldmann reference (1993) led to the algorithm disclosed in the evidentiary Waldmann et al. (1995) reference as it reads on determining / dosing regimen aspects of the claimed methods; it would have been inherent that the dosing and amount of ^{90}Y anti-Tac antibody administered to the ATL patients as well as the level of soluble IL-2R in these ATL patients of the Phase I studies would meet at least one, if not various points, of the claimed dosage / amount / soluble level determinations and regimen encompassed by claimed methods.

It is noted that it appears that pages 13-14 and pages 52-54 (Example 17) of the instant specification also acknowledge that the algorithm associated with the claimed dosing regimen was based on the in vivo pharmacokinetic and bioavailability studies during the Phase I trial using ^{90}Y anti-Tac antibody therapy. As indicated previously; it appears that the prior art and the instant application rely upon the same Phase I dose escalating trial of treating adult T cell leukemia patients with ^{90}Y anti-Tac antibody therapy.

Appellant acknowledges that Vriesendorp describe different labeling procedures for chelating indium and yttrium for radiolabeling antibodies or radicimmunoglobulin therapy for Hodgkin's disease patients; but appellant argues that Vriesendorp does not indicate which of the methods were used to chelate yttrium, nor is there any indication as to why there is such a broad range of radioactivity per mg of antibody.

It is noted that Vissendorf et al. (Int. J. Radiation Oncology 22:37-45, 1991) has been provided to support that the inherency of prior art teaching of 5 - 15 mCi doses of ^{90}Y anti-Tac antibody (see page 1711, column 1, paragraph 1 of Waldmann, Blood 1993) encompassed the total amount of 2-20 mg anti-Tac encompassed by the claimed methods in contrast to 20 - 50 mg of unlabeled antibody. The key to radiolabeling therapeutic antibodies was to achieve a therapeutic ratio by achieving high specific activities of such radioimmunnoconjugates wherein response rates are higher and toxicity is less (see Discussion of Vissendorf et al.). This is often based upon and is certainly an outcome of pharmacokinetic and bioavailability observations of clinical trials, such as the dose-escalation clinical trial taught by the primary Waldmann et al. (1993) reference.

With respect to obviousness, appellant argues that the skilled artisan could not determine the correct dose of ^{90}Y conjugated anti-Tac antibody based upon the Waldmann et al. (1993) reference.

Appellant asserts that the primary Waldmann et al. reference does not teach or suggest the use of low doses of anti-Tac antibody (less than 20 mg per dose) nor that ^{90}Y anti-Tac antibody can be used at the claimed dosage ranges having the claimed levels of radioactivity.

With respect to 20 mg per dose; it is noted that when the prior art teaches a range within, overlapping or touching the claimed range; the prior art anticipates claimed range; provided the reference teaches the range with sufficient specificity and the range disclosed in the reference and claimed by applicant overlap in scope . See Ex parte Lee 31 USPQ2d 1105 (BPAI 1993). See MPEP 2131.03.

Appellant asserts that the skilled artisan could not conclude that there was a correlation between soluble IL-2R levels and unlabeled anti-Tac dosage, let alone ^{90}Y anti-Tac antibody.

For example, appellant asserts that it would not readily apparent to the ordinary artisan that 5- 15 mCi of ^{90}Y anti-Tac antibody should be administered to a patient if and only if the patient has soluble IL-2R levels of over 50,000 U/ml from a reference that does not make any correlation to soluble IL-2R levels and does not teach the use of labeled anti-Tac antibody in any particular amount.

Here again, appellant focuses on the dosing determination / regimen as claimed and focuses on the use of unlabeled anti-Tac antibody cited in the primary reference Waldmann et al. (1993)

Even if appellant assumes that the claimed methods are drawn to treating patients at single points within the claimed dosing regimen; appellant argues the prior art Waldmann et al. (1993) reference does not show any one patient having soluble IL-2R levels being treated with a certain amount (mg) of ^{90}Y anti-Tac antibody.

Again while appellant focuses on the instant methods and disclosure of controlling the quantity of antibody administered; the evidentiary references are provided to indicate that the quantity of the prior art 5 - 15 mCi doses of ^{90}Y anti-Tac antibody would fall into at least one of the claimed limitations.

This prior art study of treating ATL patients with 5 - 15 mCi doses of ^{90}Y anti-Tac antibody taught by Waldmann et al. (1993) appears to rely upon the same or nearly the same ATL patients with the same or nearly the same levels of soluble IL-2R with the same or nearly the same amounts of ^{90}Y anti-Tac antibody in the Phase I dose escalation trial of treating ATL patients disclosed in Example 11 of the instant specification in treating ATL (see pages 41-42 of the instant specification). Also, as pointed out previously and herein, it is noted that it appears that pages 13-14 and pages 52-54 (Example 17) of the instant specification also acknowledges that the algorithm associated with the claimed dosing regimen was based on the in vivo pharmacokinetic and bioavailability studies during the Phase I trial using ^{90}Y anti-Tac antibody therapy. As indicated previously and herein; it appears that the prior art and the instant application rely upon the same Phase I dose escalation clinical trial of treating adult T cell leukemia (ATL) patients with ^{90}Y anti-Tac antibody therapy.

Again, Waldmann et al. (1993) teach administering 5 - 15 mCi doses of ^{90}Yttrium (^{90}Y) - labeled anti-Tac antibody to achieve remission in treating adult T cell leukemia patients in a dose-escalation trial (see page 1711, column 1, paragraph 1 of Waldmann, Blood 1993) including the determination of soluble IL-2R levels, encompassed by the claimed methods (see entire document, including Materials and Methods such as the Therapeutic Study Plan, Results including Tables 1 and 2, Discussion).

As appellant acknowledges; page 1710, column 1, paragraph 1 of Waldmann et al. (1993) discloses that "using radiolabeled anti-Tac antibody in conjunction with unmodified anti-Tac antibody, only 2-17 mg. of infused anti-Tac antibody per patient is required to yield circulating bioavailable anti-Tac antibody that can bind to Tac expressing ATL cells" and that page 1711, column 1, of Waldmann et al. (1993) describes that "conjugating anti-Tac with cytotoxic agents, such as 5-15 mCi ^{90}Yttrium., was employed to improve the effectiveness of IL-2R-directed therapy of ATL".

Therefore, in the alternative, it would have obvious to give 20 mg of anti-Tac antibody comprising 5-15 mCi ^{90}Yttrium to patients with soluble IL-2R levels of greater than 50,000 given the clinical results/duration of the different patients in these studies. Given the therapeutic effects or remissions of treating adult T cell leukemia as taught by the reference, it would have been understood by the ordinary artisan at the time the invention was made that the specific and therapeutic activity of providing 5-15 mCi ^{90}Y-labeled anti-Tac antibodies would encompass a certain amount (mg) of anti-Tac antibody and that the targeted adult T cell leukemia patient population would have had elevated levels of soluble IL2R, to the extent that at least one, if not more, points across the claimed regimen would have met by the successful prior art treatment of adult T cell leukemia with 5-15 mCi ^{90}Yttrium. From the teachings of the reference, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary

Rejection Under 35 U.S.C. § 103

Claim 27 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over Waldmann (Blood 82: 1701-1712, 1993) AND/OR Waldmann et al. (Important Adv. Oncol. 131-141, 1994) AND/OR Waldmann (Leukemia 7, Suppl 2 : S151-S156, 1993) AND/OR Waldmann (Ann. Oncol. 5: 13-17, 1994) in view of Vissendorf et al. (Int. J. Radiation Oncology 22:37-45, 1991) and Rubin et al. (Ann. Int. Med. 113: 619 - 627, 1990).

Appellant's arguments have been fully considered but are not found persuasive essentially for the reasons of record.

Appellant argues that the Waldmann articles simply mention 5-15 mCi doses of ^{90}Y anti-Tac antibodies.

Appellant argues that Waldmann et al. (Important Advances in Oncology 1994) describes µg amounts of ^{90}Y, which is three orders of magnitude below that claimed (µg versus mg). Given the other teachings by Waldmann et al. of record and cited herein, where it appears that the same or nearly the same ^{90}Y anti-Tac clinical trials are disclosed; the disclosure of µg amounts of ^{90}Y anti-Tac antibody was clearly a typographical error on the part of the Important Advances in Oncology 1994). For example, this Waldmann (Imp. Adv. Oncol.) reference authored by applicant appears to teach the use of same 5-15 mCi ^{90}Y-labeled anti-Tac antibody disclosed in Waldmann (Leukemia, 1993, cited as reference 22 in Waldmann, Important Adv. Oncol., 1994 and of record) (see page S154, column 1 or Leukemia, 1993) and which appears to be the same recitation of Waldmann (Ann. Oncol., 1994; page 16, column 1 paragraph 2) relied upon above in the previous section. Therefore, the reference disclosure of 5-15 µCi of ^{90}Y-labeled anti-Tac antibody appears to be a mistake and should be 5-15 mCi ^{90}Y-labeled anti-Tac antibody, as the reference clearly indicates by its own citation as well as by applicant himself

Appellant argues that neither Waldmann (Ann. Oncol. 1994) nor Waldmann (Leukemia 1993) teach specific anti-Tac antibody dosages.

Appellant asserts that there is no teaching or suggestion of the amount of antibody in milligrams, the radiation dosage is contained in, nor is there any suggestion of the soluble IL-2 receptor levels of the patients.

More importantly, appellant asserts that there is no suggestion of the relationship between radiation dosage, the amount of antibody in mg and the level of soluble IL-2R.

Appellant also asserts that there is no teaching or suggestion of the correlation between dosage and soluble IL-2R levels and that Vriesendorp and Rubin do not cure the deficiencies of the Waldmann articles.

Appellant argues that Waldmann (Blood 1993) describes a broad range of soluble IL-2R levels and the statement concerning 2-17 mg anti-Tac antibody relates to a parallel study carried out to determine the minimum amount of anti-Tac necessary to detect bioavailable circulating anti-Tac antibody and this level is quite different than the amount of anti-Tac necessary and used by Waldmann (Blood 1993) to saturate soluble IL-2R to treat disease.

Again, it appears that appellant focuses on the unlabeled anti-Tac antibody studies set forth in the Waldmann articles, by asserting, in part, that these references would lead the skilled artisan to conclude that higher doses were necessary to achieve therapeutic results.

In contrast to appellant's assertions, Waldmann (blood 1993) does not limit therapeutic treatment with anti-Tac antibodies to receptor saturation, necessitating high dosage requirements.

Appellant is reminded that the prior art Waldmann references all teach a dose escalation clinical trial of administering 5 - 15 mCi doses of ^{90}Y - labeled anti-Tac antibody to achieve remission in treating adult T cell leukemia (ATL) patients and that it was known at the time the invention was made that the serum concentrations of the soluble form of IL-2Rα was elevated in patients with disorders encompassing lymphoid neoplasia, select autoimmune diseases and in individuals rejecting allografts (see citations above).

Appellant is reminded that Waldmann articles disclose the advantages of radioimmunoconjugates comprising radiolabeled ^{90}Y - labeled anti-Tac antibody to augment the cytotoxic effects of anti-Tac antibodies as well as the advantages of overcoming human anti-mouse antibody (HAMA) responses by employing the less immunogenic humanized anti-Tac antibodies to treat patient populations with IL-2R-receptor-expressing neoplasias. (See citations above).

Therefore, given the efficacy or remissions of treating adult T cell leukemia patients in the dose-escalation Phase I trials with ^{90}Yttrium (^{90}Y) - labeled anti-Tac antibody disclosed by Waldmann; it would have been readily apparent that such radioimmunoconjugates were more effective than unlabeled anti-Tac antibodies and that less not more anti-Tac antibody would have been used to achieve clinical results or remissions.

Instead of relying upon the immunological effects of antibodies per se (e.g. ADCC or complement-mediated lysis) by the administration of unconjugated anti-Tac antibodies; the Waldmann articles all indicate the increased anti-tumor efficacy of using ^{90}Yttrium (^{90}Y) - labeled anti-Tac antibody, wherein said ^{90}Y - labeled anti-Tac antibody provides anti-tumor effects by providing the radioactive ^{90}Yttrium (^{90}Y).

It is noted that Vriesendorp notes that it was the radiation effect rather than an immunological effect of the radioimmunoconjugate that provides for the anti-tumor response. (See page 5891, column 1, paragraph 1).

In contrast to appellant's assertions, receptor saturation may be an issue with respect to unlabeled anti-Tac antibodies, but receptor saturation is not necessarily a requirement of radioimmunoconjugates nor necessarily a claimed limitation.

Here, the prior art Waldmann articles clearly teach the clinical anti-tumor effects of ^{90}Y - labeled anti-Tac antibody, wherein the amount of bioavailable anti-Tac antibody was within the ranges encompassed by the claimed methods and the efficacy of such ^{90}Y - labeled anti-Tac antibody relied upon the cytotoxic effects of the ^{90}Y radiolabel, rather than relying solely upon receptor saturation.

T he range of 2-100 mg of anti-Tac antibody provided with 5-15 mCi ^{90}Y-labeled anti-Tac antibody recited in the claims is a broad range as well as 25-75% saturation of total IL-2 receptors and surely would have been encompassed by the use of the same 5-15 mCi ^{90}Y-labeled anti-Tac antibody disclosed in the prior art. Appellant has not provided objective evidence to indicate that the prior art teachings do not meet the effective dosages including the saturation of IL-2 receptors encompassed by the claims.

Appellant acknowledges that Vriesendorp describe different labeling procedures for chelating indium and yttrium for radiolabeling antibodies or radioimmunoglobulin therapy for Hodgkin's disease patients; but appellant argues that Vriesendorp does not indicate which of the methods were used to chelate yttrium, nor is there any indication as to why there is such a broad range of radioactivity per mg of antibody.

It is noted that Vissendorf et al. (Int. J. Radiation Oncology 22:37-45, 1991) has been provided to indication that it would have been expected that the prior art teaching of 5 - 15 mCi doses of ^{90}Y anti-Tac antibody (see page 1711, column 1, paragraph 1 of Waldmann, Blood 1993) encompassed the total amount of 2-20 mg anti-Tac encompassed by the claimed methods in contrast to 20 - 50 mg of unlabeled antibody. The key to radiolabeling therapeutic antibodies was to achieve a therapeutic ratio by achieving high specific activities of such radioimmunnoconjugates wherein response rates (e.g. anti-tumor responses) are higher and toxicity is less (see Discussion of Vissendorf et al.). This is often based upon pharmacokinetic and bioavailability observations of clinical trials, such as the dose-escalation clinical trial taught by the primary Waldmann et al. articles.

Appellant's reliance on page 42, lines 14-18 for controlling the concentration or quantity of anti-Tac antibody is acknowledged, but this procedure does not appear to be distinguished from the same or nearly the same procedures generally practiced by the ordinary artisan at the time the invention was made, particularly by those artisans providing radioimmunoconjugates to human patient populations.

Appellant's arguments concerning the correlation between soluble IL-2R levels and a particular dosage of ^{90}Y anti-Tac antibody, is acknowledged.

Again, as pointed out previously and herein for examination purposes given the claimed recitation; all that is required of the prior art is to provide a dosage of mCi and an amount of ^{90}Y-conjugated anti-Tac antibody to a patient with one of the soluble IL-2R levels.

It is not necessary that the prior art provide all of the dosages and amounts and ^{90}Y-conjugated anti-Tac to a patient with all of the soluble IL-2R levels; nor it is necessary for the prior art to predetermine each of the three dosage/amount/soluble level determinations set for in the claimed methods.

Appellant's claimed methods recite various levels of ^{90}Y anti-Tac antibody based in patients having different soluble IL-2R levels. The prior art does not have to meet each asserted level, provided it meets one of the ranges of ^{90}Y anti-Tac antibody / soluble IL-2R levels.

Given the treatment of human patients who express IL-2R-expressing disorders and the nature of clinical trials; it would have been routine for the ordinary artisan at the time the invention was made to determine soluble IL-2R prior to treating or administering ^{90}Y-conjugated anti-Tac antibody to such patients.

Further, the Waldmann articles all disclose the association of IL-2 receptors and various diseases encompassed by the claimed invention as well as it was important to maintain the activity levels of anti-Tac antibody therapies in treating such diseases (see entire documents). The combined references of record also address the importance of pharmacokinetic analyses. Therefore, it would have been obvious to one of ordinary skill in the art to select for appropriate amounts of radiolabeled ^{90}Y anti-Tac antibody (e.g. mg and mCi of anti-Tac antibodies) in vivo to achieve therapeutic efficacy in the face of soluble IL-2 receptors in patients. It would have been recognized that there would have been a range of therapeutic doses since differences in the nature of diseases as well as individual patients were known and expected in the art at the time the invention was made.

Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to administer a dosage of mCi and an amount of ^{90}Y-conjugated anti-Tac antibody to a patient with one of the soluble IL-2R levels encompassed by at least one of the three parameters encompassed by the claimed methods to treat and achieve remission in patients with hematologic IL2R-expressing malignancies. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention was a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Appellant's arguments are not found persuasive.

(12) For the above reasons, it is believed that the rejections should be sustained.

Respectively submitted,

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